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PRACTICE GUIDELINE

Patient indications for Mohs micrographic surgery: a clinical practice guideline

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ABSTRACT

Objective The purpose of the present work was to develop evidence-based indications for Mohs micrographic surgery in patients with a diagnosis of skin cancer.

Methods The guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care, together with the Melanoma Disease Site Group and the Surgical Oncology Program, through a systematic review of relevant literature, patient- and caregiver-specific consultation, and internal and external reviews.

Recommendation 1 Given a lack of high-quality, comparative evidence, surgery (with postoperative or intraoperative margin assessment) or radiation (for those who are ineligible for surgery) should remain the standard of care for patients with skin cancer.

Recommendation 2 Mohs micrographic surgery is recommended for patients with histologically confirmed recurrent basal cell carcinoma of the face and is appropriate for primary basal cell carcinomas of the face that are larger than 1 cm, have aggressive histology, or are located on the H zone of the face.

Recommendation 3 Mohs micrographic surgery should be performed by physicians who have completed a degree in medicine or equivalent, including a Royal College of Physicians and Surgeons of Canada Specialist Certificate or equivalent, and have received advanced training in Mohs micrographic surgery.

Key Words Mohs, MMS, excision, surgery, radiation, practice guidelines

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INTRODUCTION

Skin cancer is the most common cancer in Canada. Skin cancer can be divided into cutaneous melanoma, non-melanoma skin cancer (NMSC), and cutaneous lymphoma. Although there are many types of NMSC, most patients present with basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), and so many clinicians consider NMSC to be synonymous with BCC and SCC as a group.

Mohs micrographic surgery (MMS) is the most common method of combined surgical excision and intraoperative margin assessment in North America. An outpatient procedure, MMS has two main components:

- removal of the skin cancer in a minor surgical room, and
- rapid processing of the specimen by a dedicated onsite histology laboratory.

Cancer Care Ontario's Program in Evidence-Based Care (PEBC), together with the Melanoma Disease Site Group and the Surgical Oncology Program, developed the present guideline, which sets out recommendations for the use of MMS in patients with skin cancer. Adjuvant radiotherapy is not considered in this guideline, which also excludes brachytherapy, because that approach is not routinely used for skin cancer in Ontario. The guideline does not address the treatments typically used for lower-risk skin cancers, such as destructive techniques (electrodesiccation and curettage, cryotherapy, photodynamic therapy, topical therapy, injectable treatments).

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METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[1,2]. The process includes a systematic review, with interpretation of the evidence by the authors, who then draft recommendations based on the evidence and expert consensus; an internal review by content and methodology experts; and an external review by clinicians and other stakeholders. The authors of the present guideline had expertise in MMS, dermatology, head-and-neck surgery, pathology, radiation oncology, medical oncology, and health research methods.

Further details of the methods and findings of the systematic review that informed the recommendations set out here have been published elsewhere[3,4]. Briefly, MEDLINE, EMBASE, and the Cochrane Library were searched for studies comparing MMS with either wide local excision (WLE) or radiation; studies comparing WLE with radiation; prospective or retrospective studies assessing outcomes after MMS that had performed multivariate analyses; and studies assessing surgical volumes for MMS. Studies were assessed for quality using components of the Cochrane Risk of Bias tool (https://methods.cochrane.org/bias/) for randomized controlled trials (RCTs) and the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions, http://www.riskofbias.info) for non-RCTs.

Patient- and Caregiver-Specific Consultation Group

A combination of patients, survivors, or caregivers participated as consultation group members. They reviewed the project plan and provided feedback about its comprehensibility, appropriateness, and feasibility to the Working Group's health research methodologist. The health research methodologist relayed the feedback to the Working Group for consideration.

Internal Review

Guidelines from PEBC are reviewed by a panel of content experts (the Expert Panel) and a methodology panel (the Report Approval Panel).

The Expert Panel consisted of Mohs micrographic surgeons, dermatologists, head-and-neck surgeons, plastic surgeons, pathologists, radiation oncologists, and medical oncologists. At least 75% of the Expert Panel must vote on whether they approve the document, and of those that vote, 75% have to approve the document. All members of the Report Approval Panel have to approve the document.

The Working Group was responsible for incorporating the feedback from both panels.

External Review

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft guideline from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guideline to Ontario practitioners. Feedback from the professional consultation was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. All surgeons and plastic surgeons in the PEBC database with an interest in the head and neck, and any clinicians with an interest in the head and neck, melanoma, or skin, were contacted by e-mail.

RESULTS

The full systematic review provides details of the methodologic characteristics and clinical outcomes.[3,4]

Patient- and Caregiver-Specific Consultation Group

The consultation group had the participation of 4 individuals who were patients, survivors, or caregivers.

Internal Review

In April 2017, 3 Report Approval Panel members, including the PEBC Director and 2 methodology experts, reviewed and approved the draft guideline.

In July 2017, 17 of the 20 members of the Expert Panel (85%) cast votes, and none abstained. Of those who cast votes, 13 (76.5%) approved the document.

External Review

After approval of the document at internal review, the authors circulated the draft document to external review participants for review and feedback. The Working Group identified 11 clinical experts from North America to act as targeted peer reviewers. Of the 11, 5 agreed to be the reviewers; 4 responses were received. Table I summarizes the survey results.

For the professional consultation, 65 individuals who practice in Ontario were contacted, resulting in 9 (13.8%) responses. Of those 9, 3 said that they were no longer in active practice, and 1 was not willing to participate. Table II summarizes the results of the survey responses from the remaining 5 professionals.

RECOMMENDATIONS AND KEY EVIDENCE

The target population for this guideline is adults with a diagnosis of skin cancer. The intended users of this guideline are clinicians involved in the assessment and treatment of patients with skin cancer.

Aside from MMS, other methods of intraoperative peripheral and deep circumferential margin analysis are available and are also expected to provide advantages in comparison with standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and does not cover other forms of non-MMS frozen-section margin control. Further, this guideline refers to radical radiotherapy; adjuvant radiotherapy was not considered in the literature review. Similarly, metastatic disease was not addressed.

Recommendation 1

Given a lack of high-quality comparative evidence, surgery (with postoperative or intraoperative margin assessment) or radiation (for those who are ineligible for surgery) should remain the standard of care for patients with skin cancer.

Qualifying Statements

Eligibility for surgery depends on disease stage, surgical considerations, esthetic outcomes, patient comorbidities, and patient preference.

TABLE I Responses to nine items on the targeted peer reviewer questionnaire

Question	Reviewer ratings (*n*=4)				
	Lowest quality 1	2	3	4	Highest quality 5
Rate the guideline development methods.	0	1	0	1	2
Rate the guideline presentation.	0	0	0	2	2
Rate the guideline recommendations.	0	1	0	2	1
Rate the completeness of reporting.	0	1	0	1	2
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	1	0	2	1
Rate the overall quality of the guideline report.	0	0	1	2	1
	Strongly disagree 1	2	Neutral 3	4	Strongly agree 5
I would make use of this guideline in my professional decisions.	1	0	0	2	1
I would recommend this guideline for use in practice.	1	0	0	1	2

What are the barriers or enablers to the implementation of this guideline report?

- Access to Mohs micrographic surgery in Ontario
- Accessibility of guideline to practitioners and patients
- Accessibility and awareness of Mohs micrographic surgery to clinical experts in the field

TABLE II Responses to four items on the professional consultation survey

General questions	Overall guideline assessment (*n*=5)				
	Lowest quality 1	2	3	4	Highest quality 5
Rate the overall quality of the guideline report.	0	1	0	3	1
	Strongly disagree 1	2	Neutral 3	4	Strongly agree 5
I would make use of this guideline in my professional decisions.	0	1	1	2	1
I would recommend this guideline for use in practice.	0	1	0	1	3

What are the barriers or enablers to the implementation of this guideline report?

- Availability of and access to Mohs micrographic surgery in Ontario
- Lack of resources—most hospitals in Ontario do not provide Mohs micrographic surgery
- Access to Mohs training

There are clinical situations in which referral to a radiation oncologist might be considered appropriate. Based on standards of care and clinical experience, the Working Group suggests that referral for radical radiotherapy might be appropriate in these clinical situations:

- When the patient expresses a preference based on the expected cosmetic or functional outcomes of surgery or anxiety related to surgery
- For patients in whom surgery is associated with an increased risk of recurrence or extensive subclinical spread

Further indications for patients with skin cancer who would be eligible for radiation are beyond the scope of this guideline.

A multidisciplinary approach is also suggested for high-risk cases.

For characteristics of patients who would be considered appropriate for referral to a Mohs surgeon, please refer to Recommendation 2.

Key Evidence

The evidence comes from three retrospective studies comparing surgical excision with radiotherapy in patients with SCC of the lip. No published evidence has compared MMS with radiation.

First, a trial by de Visscher *et al.*[5] in previously untreated patients reported similar local recurrence rates for surgery and radiotherapy (3.6% and 4.4% respectively, $p > 0.05$). The arms differed statistically in terms of tumour size,

differentiation, and years of follow-up, and compared with patients in the surgery group, those in the radiotherapy group had tumours that were larger in size. Regional recurrence rates were significantly lower after surgery than after radiotherapy (4.8% and 12.2% respectively, $p = 0.03$), but only tumour size carried significance in the adjusted analysis.

In the remaining two studies, methods and results were unclear and should be interpreted with caution. Babington *et al.*[6] reported recurrence rates of 53% for surgery and 19% for radiotherapy. A *p* value was not reported. Of enrolled patients, 20% had been treated elsewhere previously, and many were referred with recurrent disease. However, the distribution of the patients within the surgery and radiation arms is unclear. Polytomous regression analysis reported that a close (≤2 mm) or positive margin in the surgery group predicted local recurrence ($p = 0.05$).

The study by Sarachev *et al.*[7] reported local recurrence rates of 3.1% for surgery and 4.3% for radiotherapy. A *p* value was not reported. The study provided minimal information about the patients who received radiotherapy and about the comparability of treatment groups.

Recommendation 2

Mohs micrographic surgery is recommended for patients with histologically confirmed recurrent BCC of the face, and it is appropriate for primary BCCs of the face that are larger than 1 cm, have aggressive histology, or are located on the H zone of the face.

Qualifying Statements

There are situations in which MMS might be considered for patients outside of recommendation 2: smaller tumours (<1 cm in diameter) for which tissue-sparing is of functional or cosmetic significance (including tumours in patients with a genetic predisposition to multiple skin cancers, such as Gorlin syndrome), complex tumours that might require margin-controlled surgery, or immunosuppressed patients.

Patients with complicated BCC or locally advanced BCC should be considered for multidisciplinary assessment by dermatologists, surgical specialists, and medical and radiation oncologists.

Examples of aggressive histology include basosquamous, morpheaform or sclerosing, micronodular, and infiltrative, and lesions with perineural invasion.

The Working Group recognizes that much of the literature used to inform the recommendation is based on BCC; however, based on clinical experience and expert opinion, the Working Group suggests that, in some instances, patients with SCC might have indications the same as those for patients with BCC. However, in cases in which SCC is deemed high-risk, the need for evaluation by a multidisciplinary team (that is, dermatologists, surgical specialists, and medical and radiation oncologists) should be considered.

Patients with aggressive or high-risk NMSC could benefit from methods such as MMS or other intraoperative margin-controlled surgeries that lower recurrence rates. Radiation is also a valuable option in high-risk patients who might have a contraindication to surgery or who might need adjuvant therapy in high-risk disease.

Patients with dermatofibrosarcoma protuberans, atypical fibroxanthoma, and sebaceous carcinoma have shown benefit with the use of MMS compared with WLE. The results of the relevant studies were subject to selection bias, and the studies were not adequately powered. However, the Working Group notes that, although methodologically strong evidence does not exist for rarer types of skin cancer, MMS should be considered on a case-by-case basis.

Patients with invasive melanoma or melanoma *in situ* have shown no survival or recurrence benefit with the use of MMS over WLE. Those retrospective studies were not adequately powered. Cancer Care Ontario recently published a guideline about primary excision margins in cutaneous melanoma. Please refer to that guideline for recommended surgical margins in that population.

Key Evidence

The best evidence comes from two RCTs[8–12].

Mohs micrographic surgery has not been shown to be inferior to WLE. Moreover, selected patient populations have been shown to achieve better outcomes with MMS.

One RCT compared MMS with surgical excision for BCC[9,11,12]. That RCT included, for primary BCC, patients with a facial tumour at least 1 cm in diameter, located in the H zone, or a facial tumour of an aggressive histopathologic subtype, and for recurrent BCC, facial tumours recurring for the first or second time. For primary BCC, no statistically significant differences in the recurrence rates for MMS and for surgical excision were found at 5 years ($p = 0.397$)[9] or 10 years (MMS, 4.4%; surgical excision, 12.2%; $p = 0.100$)[12]. In the management of recurrent BCC, recurrence rates were significantly lower for MMS than for surgical excision at both 5 years ($p = 0.021$)[9] and 10 years ($p = 0.023$)[12].

Esthetic outcomes did not significantly differ between surgical excision and MMS for both primary and recurrent BCC[11]. However, for tumours that required more than 1 surgical excision (primary BCC, 18%; recurrent BCC, 32%) or at least 2 MMS stages for complete excision, defects were significantly larger after surgical excision than after MMS in both primary ($p < 0.001$) and recurrent ($p = 0.026$) BCC[11]. For primary and recurrent BCC, cosmetic results were significantly poorer as the defect size increased.

A significant difference in the number of complications was found between MMS (8%) and surgical excision (19%) for patients with recurrent BCC ($p = 0.021$). No difference in complications was found for patients with primary BCC ($p = 0.681$).

Although the results were not statistically significant for recurrence rates after 10 years of follow-up for patients with primary BCC, the Working Group suggests that clinicians consider the value of cosmesis in addition to recurrence rates.

The second RCT involved 30 patients with high-risk BCC. The authors reported that the median area of surgical defects was significantly smaller after MMS than after standard surgery (MMS, 116.6 mm^2; surgical excision, 187.7 mm^2; $p < 0.001$)[10]. The trial closed before accrual completion because the predetermined endpoint demonstrating a significant difference in mean defect diameter by a factor of 1.5 was reached.

Three observational studies (one prospective, two retrospective) compared MMS with surgical excision in patients with BCC and SCC[13–15]. Two studies found no

statistical difference in recurrence rates between MMS and surgical excision[13,15]; the third did not report a *p* value[14]. However, the studies were not powered to detect differences, and the design of the studies allowed for selection bias. The retrospective study by van der Eerden *et al.*[15] found that, in recurrent NMSC of the nose, defects were smaller after MMS ($p = 0.038$), a finding that remained true after adjustments for localization and for primary or recurrent disease ($p = 0.008$).

In the retrospective single-arm study by Flohil *et al.*[16], a multivariate analysis of patients with BCC of the head and neck who had received MMS found that BCCs located in the H zone, tumours larger than 10 mm, aggressive tumour subtypes, and recurrent tumours remained significantly associated with a requirement for 2 or more stages of MMS. Tumour size (≥21 mm), recurrent tumours, and tumours in the H zone remained significant predictors for extensive subclinical tumour spread.

In another retrospective single-arm study by Batra *et al.*[17] of 1131 patients with malignant skin tumours treated using Mohs, a multivariate analysis found that the most significant predictors of extensive subclinical spread were any type of BCC on the nose, increased preoperative lesion size (≥10 mm), recurrent BCC on the nose, and location on the ear or eyelid.

Three retrospective comparative studies have shown benefit for the use of MMS (compared with WLE) in patients with dermatofibrosarcoma protuberans. In one, the difference was statistically significant ($p = 0.016$)[18]; in the other two, one of which used the Mohs Tübingen technique, no *p* value was reported[19,20]. Retrospective comparative studies on atypical fibroxanthoma (*p* value not reported)[21] and sebaceous carcinoma (*p* value not reported)[22] have also shown benefit for the use of MMS compared with WLE. The results of those studies are subject to selection bias, and the studies were not powered to detect differences between treatment groups.

Two retrospective comparative studies showed no benefit for the use of MMS (compared with WLE) in patients with invasive melanoma[23] or melanoma *in situ*[24]. Those studies were not powered to detect differences between treatment groups.

Recommendation 3

Mohs micrographic surgery should be performed by physicians who have completed a degree in medicine or equivalent, including a Royal College of Physicians and Surgeons of Canada specialist certificate or equivalent, and have received advanced training in MMS.

Qualifying Statements

The MMS technique requires specific training in the assessment of frozen-section histology to detect cutaneous malignancies, the surgical skills of cancer removal, and the reconstruction of cosmetically sensitive areas of the face and other complex areas.

Advanced training is defined as having a recognized MMS fellowship through the American College of Mohs Surgery or equivalent accrediting body.

Key Evidence

No studies of associations between MMS surgical volume or training and patient outcomes were found.

This recommendation was based on the acknowledgment by the Working Group of the unique, specialized skills required for successful conduct of MMS procedures that would not be acquired in a current Royal College of Physicians and Surgeons of Canada specialist certificate.

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CONFLICT OF INTEREST DISCLOSURES

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We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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